REMARKS

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Claims 1-43 were pending. The Examiner withdrew 25-43 from consideration following a restriction requirement. Claims 1-24 were rejected in the previous Office action, and no claims were allowed. Claim 18 is amended herein. It is believed that no new matter has been added. Claims 1-24 are presently pending.

The "Cross Reference to Related Applications" section of the specification has been amended to reflect the issuance of U.S. Application Serial Nos. 09/361,775 and 09/113,947 as U.S. Patent Nos. 6,462,019 and 6,410,512, respectively.

Formal Matters

The Examiner has stated that references not considered with the IDS received July 16, 2001 because the references were not in Examiner's file. Applicant respectfully submits that

> a copy of any patent, publication, pending U.S. application, or other information listed in an information disclosure statement is not required to be provided if: (1) the information was previously cited by or submitted to, the Office in a prior application, provided that the prior application is properly identified in the IDS and is relied on for an earlier date under 35 U.S.C. § 120 ...

Manual of Patent Examination Procedure § 609 III(A)(2) (8th ed. 2001). Applicants have previously submitted all of the references not considered in the instant application in related applications, and thus are in full compliance with the IDS requirements under § 609 of the *Manual of Patent Examination Procedures*. Furthermore, Applicants note that recent correspondence with Dr. Wityshyn indicated that the IDS box for the related application 09/421,545 was recently brought to the Examiner's attention. Nonetheless, Applicants have again enclosed herewith courtesy copies of these references to expedite prosecution.

Applicants respectfully remind the Examiner of the mandate regarding a speedy prosecution by the Patent & Trademark Office. According to the MPEP, "the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied" to "bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public." MPEP § 706.07. "[I]t is to the interest of the applicants as a class as well as to that of the public that prosecution of an application be confined to as few actions as is consistent with a thorough consideration of its merits." *Id.* Furthermore, Applicants note that the failure to examine the references properly submitted in the IDS of properly identified related applications precludes the next Action being a Final Action if the examiner introduces a new ground of rejection based on the properly submitted references. MPEP § 706.07(a).

Both essential and nonessential subject matter may be incorporated by reference to prior filed, commonly owned U.S. applications. MPEP § 608.01(p)(I)(A). The alleged improperly incorporated references are (1) U.S. Patent Application Serial No. 08/458,434 (page 19, line 10 and page 34, line 2), and (2) U.S. Patent Application Serial No. 09/096,631 (page 4, line 14 and page 26, line 5). First, U.S. Patent Application Serial No. 08/458,434 has issued as U.S. Patent No. 6,083,690 on July 4, 2000. Applicants respectfully request that the Examiner amend the specification to reflect the issuance of this patent. MPEP § 1302.04(f). Second, U.S. Patent Application Serial No. 09/096,631 is a co-pending application assigned to Osteoscreen, Inc. Osteoscreen is the common owner of the instant application and the co-pending Application Serial No. 09/096,631. Therefore, the co-pending application has been properly incorporated by reference.

The Action objected to the name of inventor Rossini appearing without a full first name. A Petition under 37 C.F.R. § 1.182 to correct the above-named inventor to that of Giovanni Rossini is enclosed as well as a Substitute Declaration and the required fees.

The Action objected to the title because the title of the invention is allegedly not aptly descriptive. The title has been amended.

The Action also objected to the abstract of the disclosure because of legal phraseology. The abstract has been amended.

In light of the above, Applicants respectfully submit that the objection to the specification has been overcome. Therefore, Applicants request the withdrawal of the objections.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 1-24 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Action, no mention is made in the specification as filed of a compound that does not inhibit the isoprenoid pathway nor how to find such a compound. The Action asserts that the claims are not limited to compounds that inhibit proteasomal activity and enhance bone formation, thus requiring undue experimentation to determine what compounds would work in the invention. The Action also alleges that the specification is enabled for PSI, MG132, and epoxomicin, but not does not reasonably provide enablement for "a compound." Applicants respectfully traverse these rejections.

1. The specification has supporting written description for the administration of a compound that inhibits proteasomal activity but does not inhibit the isoprenoid pathway.

Applicants respectfully request the attention of the Examiner to the following passages in the original specification:

(a) "The compounds that are useful in the methods and compositions of this invention are ***inhibitors of proteasomal activity*** ..." Specification, Page 25, Lines 23-24 (emphasis added). "The compounds, thus identified, which are used according to the method of the invention as it relates to treating bone defects, however, preferably ***do not include compounds that inhibit the isoprenoid pathways*** ..." Specification, Page 26, Lines 1-3 (emphasis added).

(b) "As set forth above, in preferred embodiments of the methods of the invention, the identified compounds used in treatment of bone disorders are ***other than statins and other***

compounds that inhibit the isoprenoid pathway, typically as shown in Figure 1."

Specification, Page 29, Lines 20-22 (emphasis added).

Applicants submit that a person of skill in the art would recognize in the disclosure a description of the invention defined by the claims. Applicants respectfully request that the Examiner present evidence or reasoning why persons of skill in the art would not recognize the exclusion of compounds inhibiting the isoprenoid pathway based on the written description cited *supra*. *See* MPEP § 2163.04 (II) ("the examiner has the initial burden of presenting evidence or reasoning to explain why persons of skill in the art would not recognize in the disclosure a description of the invention defined by the claims").

2. The claims are properly limited to the genus of compounds that inhibit proteasomal activity or NF-kB.

There is no requirement that the methods provided in the specification be limited to the embodiments and examples disclosed therein. The instant claims are directed to the use of a genus of compounds that are inhibitors of proteasomal or NF-κB activity, as an anabolic treatment for bone. The genus is exemplified with numerous species disclosed in the specification. Thus, the claims are not limited to the disclosed species, but rather to the genus of compounds useful in the claimed method. Applicants note that

> [f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.

MPEP § 2164.02. As required, Applicants provide representative examples in the specification. Applicants also provide a statement applicable to the genus as a whole. For example, the specification discloses that "we have discovered that inhibition of the functions of the proteasomal proteins and, to a lesser extent, of NF-κB in bone cells leads to increased bone growth ... Thus, assessing a candidate compound for its ability to inhibit proteasomal proteins or NF-κB provides a useful means to identify bone ... anabolic agents." *See* specification, at page

7, line 29 to page 8, line 5. "Once a compound found to inhibit these activities has been identified, it can be used in ... a method to stimulate the growth of bone ... by contacting suitable cells with the identified compound." *See* specification, at page 8, line 13-15.

3. The Examiner has not providing evidence or technical reasoning substantiating the assertion that the specification is not enabled.

The instant Action contains no discussion or analysis regarding the conclusion of non-enablement asserted by the Office. The Action is devoid of any specific findings of fact or any evidence supporting such facts. Rather, the Action recites the Wands factors with findings of fact or analysis. "Proof of enablement will required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the claimed genus as a whole without undue experimentation." MPEP § 2164.02 (emphasis added). Applicants respectfully submit that the Office make findings of fact and provide the required analysis to support the conclusion of non-enablement. If the Examiner is aware of specific findings of fact related to enablement, Applicants request the communication of such facts.

4. The specification fully enables the genus of compounds that are proteasomal inhibitors and induce bone growth.

Applicants respectfully submit that the enablement requirement of 35 U.S.C. § 112, first paragraph does not require a complete absence of experimentation in the practice of the claimed invention. Routine experimentation using well known and conventional methods does not constitute undue experimentation. *Johns Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705 (1998). In light of the guidance in the specification, the working examples, and what is well known in the art, the practice of the claimed methods using the genus of claimed compounds meets the requirement of disclosing how to make and use the methods under 35 U.S.C. § 112, first paragraph.

The specification provides adequate guidance and working examples. The specification teaches the skilled artisan how to identify compounds useful in the claimed method, clearly disclosing the characteristics of the genus of compounds useful in the claimed methods and assays to assessing such characteristics. *See, e.g.*, specification, at page 17, line 5 to page 24, line 9. Applicants further provide guidance as to the nature of the compounds useful in the claimed methods as well as identifying specific species within the genus of compounds. *See, e.g.*, the specification, at page 25, line 23 to page 33, line 20. The specification fully discloses how to use the claimed methods to the skilled artisan. *See, e.g.*, specification, at page 8, line 26 to page 17, line 3. The specification further provides working examples for the claimed methods. *See* Examples 1-7. Finally, the specification teaches the extension of the working examples to other compounds. *See , e.g.*, specification, at page 8, line 13-15.

Applicants respectfully submit that the evidence of record further demonstrates the specification as fully enabling the claimed methods. The submitted declarations of Gregory R. Mundy and I. Ross Garrett provided herein use the guidance within the specification to identify and use proteasomal inhibitors to stimulate bone growth. The steps, materials, and conditions used in the experiments of the declaration of Dr. Mundy, submitted pursuant to 37 C.F.R. § 1.132 on February 2, 2001, use the guidance provided in the specification as filed and what was well known to one of skill in the art. The Declaration of Dr. Mundy provides extensive histological and gross data confirming and extending the data presented in the working examples. The data includes the use of multiple, structurally unrelated proteasomal inhibitors to achieve statistically significant increases in bone growth (see Table 1), osteoblast proliferation (Table 2), and osteoblast differentiation (Table 3). All of the experiments set forth by Dr. Mundy use the guidance and assays disclosed in the specification. *See, e.g.*, Example 2.

The Declaration of Dr. Garrett, submitted pursuant to 37 C.F.R. § 1.132 herewith, provides an even greater array of structurally-unrelated proteasome inhibitors identified using the guidance and assays as disclosed in the specification. Using the guidance and assays provided in Example 2 of the specification, additional compounds were identified as proteasomal inhibitors

and bone growth stimulators in Table 1. Tables 2, 3, and 4 and Figure 1 further identify proteasomal inhibitors that are anabolic for bone using the guidance found in page 19, line 7 to page 20, line 10 and in Example 1 to examine the induction of BMP-2 promoter activity. Finally, Tables 5-6 and Figure 2 demonstrate further use of the guidance found in the specification at page 21, line 13 to page 24, line 9 and Examples and 7. In Tables 5 and 6, statistically significant increases in total bone area are observed after *in vivo* treatment with two proteasomal inhibitors using different routes of administration and different doses of inhibitors. Likewise, Figure 2 demonstrates a statistically significant increase in bone formation rate using additional proteasomal inhibitors administered by various routes *in vivo*.

In light of the evidence demonstrating that the full scope of claimed methods work using the guidance provided in the specification, any experimentation required to practice the claimed methods is routine. Such experimentation uses conventional and well known methods in molecular biology (*i.e.*, the determination of proteasomal inhibiting activity) and in cellular and histological techniques (*i.e., in vivo* treatment and tissue sample processing and analysis). As described above, the specification provides extensive guidance and examples for practicing the claimed subject matter. In addition, the claimed methods have actually been shown to be effective for stimulating bone growth using the guidance provided in the specification as filed. The disclosure in the specification in conjunction with the efficacy of the claimed methods demonstrate that any experimentation required for practicing the claimed methods would not be undue. Simply stated, the specification teaches all of the steps required for practicing the proven claimed methods, and all that remains is repetition of these teachings to practice the scope of the claim.

In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 112, first paragraph is overcome. Therefore, Applicants request the withdrawal of this rejection.

Rejection Under 35 U.S.C. 112, Second Paragraph

Claim 18 is rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Claim 18 is amended herein to include the fully spelled out chemical name with the abbreviations.

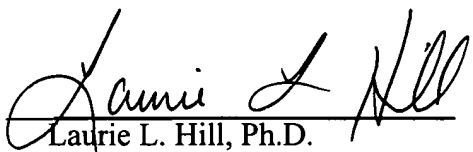
In light of the above remarks, Applicant respectfully submits that the rejection under 35 U.S.C. § 112, second paragraph is overcome. Therefore, Applicants request the withdrawal of this rejection.

CONCLUSION

Applicants submit that the objections and rejection under 35 U.S.C. § 112 have been overcome by the above amendments and remarks. Early allowance of pending claims 1-24 is respectfully requested. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing 432722002623. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 23, 2003

Respectfully submitted,

By: 

Laurie L. Hill, Ph.D.
Registration No. 51,804
Morrison & Foerster LLP
3811 Valley Centre Drive, # 500
San Diego, CA 92130-2332
Telephone: (858) 720-7955
Facsimile: (858) 720-5125